Acquired Immunodeficiency Syndrome Panels

United States

Chair

Dr. Susan Zolla-Pazner
(Chair 1999- , Member 1995-1998)
Professor, Department of Pathology
New York University School of Medicine
Scientific Director
Research Center for AIDS and HIV
Veterans Affairs Medical Center
423 East 23rd Street, Room 18124N
New York, New York 10010-5050
Telephone: (212) 263-6769
FAX: (212) 951-6321
E-mail: zollas01@popmail.med.nyu.edu

Japan

Chair

Dr. Takashi Kitamura
(Chair 1995- , Member 1988-1994)
Director
Toyama Institute of Health
17-1 Nakataikoyama, Kosugi-machi
Toyama 939-0363, Japan
Telephone: 011-81-766-56-5506
FAX: 011-81-766-56-7326
E-mail: tktoyama@p1.coralnet.or.jp

Panel Members

Dr. Irvin S.Y. Chen (1993-1998)
Division of Hematology/Oncology
Department of Medicine
UCLA Center for Health Sciences
UCLA School of Medicine
Los Angeles, California 90024

Dr. Norman Letvin (1995-1998)
Professor of Medicine
Harvard Medical School
Chief, Division of Viral Pathogenesis
Beth Israel Deaconess Medical Center
Research East-113
330 Brookline Avenue
Boston, Massachusetts 02215

Dr. Christopher J. Miller (1999-)
Professor
California Regional Primate Research Center
University of California, Davis
Hutchinson and County Road 98
Davis, California 95616-8542
Telephone: (530) 752-0447
FAX: (530) 752-2880
E-mail: cjmiller@ucdavis.edu

Dr. Masakazu Hatanaka (1990-)
Director
Shionogi Institute for Medical Science
5-12-4 Sagiso
Settsu City
Osaka 553-0002, Japan
Telephone: 011-81-6-6458-5861
FAX: 011-81-6-6458-0987
E-mail: masakazu-hatanaka@ex.shionogi.co.jp

Dr. Satoshi Kimura (-2000)
Professor
Department of Infectious Diseases
School of Medicine, University of Tokyo
7-3-1 Hongo, Bunkyo-ku
Tokyo 113-8655, Japan

Dr. Hiroshi Kiyono (1999-)Professor
Immunochemistry Laboratory
Research Institute for Microbial Diseases
Osaka University
3-1 Yamada-oka, Suita
Osaka 565-0871, Japan
Telephone: 011-81-6-6879-8292
FAX: 011-81-6878-6765
E-mail: kiyono@biken.osaka-u.ac.jp

Dr. Julie Overbaugh (1999-)
Member, Division of Human Biology
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, C3-168
Seattle, Washington 98109
Telephone: (206) 667-3524
FAX: (206) 667-1535
E-mail: joverbaug@fhcrc.org

Dr. Thomas Quinn (1988-1997)
Senior Investigator
NIAID, NIH
Johns Hopkins Hospital
600 Wolfe Street
Blalock 1111
Baltimore, Maryland 21205

Dr. Robert T. Schooley
(Chair 1995-1998, Member 1994-1999)
Professor of Medicine
University of Colorado Health Sciences Center
4200 East Ninth Avenue, CBB-168
Denver, Colorado 80262
Telephone: (303) 315-7233
FAX: (303) 315-8681
E-mail: robert.schooley@uchsc.edu

Dr. Sten H. Vermund (1999-)
Professor and Director
Sparkman Center for International Public Health Education
University of Alabama
BBRB 206
1530 Third Avenue South
Birmingham, Alabama 35294-2170
Telephone: (205) 975-7700
FAX: (205) 934-5600
E-mail: sten@uab.edu

Dr. Hiroaki Mitsuya (1999-)
Department of Medicine
Kumamoto University School of Medicine
1-1-1 Honjo
Kumamoto 860-8556, Japan
Telephone: 011-81-96-373-5156
FAX: 011-81-96-363-5264
E-mail: hmitsuya@kaiju.medic.kumamoto-u.ac.jp

Dr. Masanao Miwa (1988-1999)
Professor
Institute of Masic Medical Sciences
Tsukuba University
1-1-1 Tennodai, Tsukuba City
Ibaraki 305-0006, Japan

Dr. Kenji Soda (1995-2000)
Professor Emeritus
Director-General
Yokohama City University
Yokohama Comprehensive Care Continuum
1735 Toriyama-cho, Kohoku-ku
Yokohama 222-0035, Japan
Telephone: 011-81-45-475-0197
FAX: 011-81-45-475-0002

Dr. Kiyoshi Takatsuki (-1999)
Director
Kitano Hospital
Tazuke Kofukai Medical Research Institute
13-5 Kamiyama-cho, Kita-ku
Osaka 530-0026, Japan

Guidelines

Acquired Immunodeficiency Syndrome Panels

Before the first meeting of the Acquired Immunodeficiency Syndrome (AIDS) Panels in 1988, the Joint Delegation of the U.S.-Japan Cooperative Medical Science Program identified and adopted guidelines targeting HIV and related retroviruses as areas of research and activities of great importance for achievement of the Panels' objectives. In subsequent revisions, guidelines were added, to encourage exchange of information and collaboration between Japan and the United States. The guidelines presented here emanated from the revisions made at the seventh joint meeting of the AIDS Panels, in Kimiidera, Japan, in March 1995.

The research areas and activities important to the Panels are as follows:

1. Conduct of epidemiology and natural history studies of HIV and related retroviruses, including patterns of the epidemic as it continues to emerge in Asia, risk factors for and mechanisms of transmission, progression of disease, development of diagnostics, and development and assessment of intervention strategies

2. Study of the etiology and pathogenesis of HIV and related retroviruses, to improve basic understanding of the causative agents, including retrovirology and genetics, mechanisms of establishment of infection, cellular and molecular mechanisms of immunopathogenesis, and pathogenic mechanisms of related malignant conditions, opportunistic infections, neurological disorders, wasting, and other organ- and tissue-specific disorders

3. Development of antiviral compounds and immunomodulators for HIV infection; development of diagnostics, prophylaxis, and therapies for opportunistic infections, malignant conditions, and other conditions associated with retroviral infection; development of approaches to inhibit mother-to-child transmission of HIV; development of vaccines; and establishment of in vitro and in vivo evaluation systems, including animal models

4. Investigation of the relationship between behavior and HIV infection and disease, including risk factors for transmission, development of behavioral interventions, and behavioral aspects of clinical trials of vaccines and therapeutics

5. Exchange of basic and clinical information between investigators in Japan and the United States and sharing of techniques and materials pertinent to human retrovirus infections

6. Development of links for collaboration between junior and senior scientists in both countries and joint pursuit of research efforts

Five-Year Summary

Broad Goals

The HIV/AIDS pandemic has spread in Asia and the Pacific, but with different dynamics and features. At the beginning of the last decade, India and Thailand experienced rapid escalation of their HIV/AIDS epidemics. In the last 5 years, Thailand has made great strides in controlling this escalation, but India continues to experience growth in the prevalence of HIV/AIDS cases and may surpass the countries of sub-Saharan Africa. Epidemics of complex nature have begun in Cambodia, China, Myanmar, and Vietnam, with mixed contributions from injection drug use and heterosexual transmission. Two problems must be overcome in the Asia-Pacific region. Because of unequal economic development, all countries of the region do not equally benefit from the recent achievements of HIV/AIDS research. Antiretroviral therapies have reduced the rate of progression to clinical AIDS and death among HIV-positive persons in developed countries, but these therapies are largely unavailable in less developed nations. In addition, incomplete implementation of advanced testing procedures for screening of blood donors and for blood testing has resulted in unsafe blood supplies in many areas.

The AIDS Panels have discussed the scientific achievements obtained through Panel activities and recognize the importance of equal availability of scientific advances in Asia-Pacific settings, to improve clinical care and control of the epidemic through measures to ensure the safety of the blood supply and other prevention interventions.

The broad goals of the Panels are to (1) share scientific information and (2) initiate research collaboration, to develop scientific knowledge and tools to prevent new infections and to improve the care of persons already infected with HIV. Scientific areas of cooperation target (1) the natural history and epidemiology of retroviruses, including mucosal transmission, mucosal immunity, and genetic, host, and viral characteristics affecting transmission and pathogenesis; (2) basic studies of immunology and virology, in search of novel targets for therapeutic intervention and novel and multipotent vaccine approaches; (3) clinical research on therapeutic interventions; and (4) development of preventive interventions.

Progress and Accomplishments

Natural History, Epidemiology, and Prevention

During the last 5 years, the AIDS Panels have continued to monitor the global epidemic, as well as the epidemics in the United States and Japan. The focus has been on epidemiology in Asia and the Pacific, including Cambodia, China, India, Indonesia, Japan, Malaysia, Myanmar, the Philippines, Thailand, and Vietnam. Both Panels also have been pursuing research collaborations in the countries of sub-Saharan Africa. China, India, and Vietnam are experiencing explosive epidemics. On the other hand, the Philippines has uniquely experienced low HIV/AIDS prevalence despite high prevalence of ulcerative sexually transmitted diseases among the general population and commercial sex workers. The low prevalence of injection drug use in the Philippines may contribute to the low rate of dissemination of HIV.

In Japan, there are only several thousand cases of HIV infection due to risk factors such as heterosexual contact and injection drug use, but two alarming signs are recognizable. First, although the annual incidence of HIV positivity identified in blood donors at blood screening is not very high, it has been increasing steadily, from 0.1 cases per 100,000 donations in 1990 to 1.03 in 1999, exceeding the alarming level of 1.0/100,000 for the first time. Second, in three cases, HIV infection was acquired through receiving transfusion of blood that had been screened for antibody to HIV. This occurrence demonstrates the need to close the "window period" to prevent transmission of HIV by transfusion. During this period, donated blood may test negative for antibody even though HIV is present and can be transmitted.

In the United States, the epidemic continues to evolve, with 700,000-900,000 residents currently infected with HIV. Although the incidence of new AIDS cases has declined, this observation is largely due to expanded use of new antiretroviral therapies that prevent progression of HIV infection to AIDS. In addition, the previous decline in death rates has now stabilized. Furthermore, the rate of new HIV infections has been constant since 1990, indicating that the overall epidemic is continuing to expand. HIV infection rates are continuing to climb in a number of subpopulation groups, such as women, racial and ethnic minorities, young homosexual men, adults older than 50 years of age, and persons with addictive disorders.

Research conducted by Panel members continues to provide information on the relationship between HIV transmission and a variety of viral and host factors, such as viral subtype, viral load, host genetic factors, the presence of sexually transmitted diseases, circumcision, and breast-feeding. Study findings demonstrate that viral load is the best predictor of HIV transmission. Lowering viral load

through antiretroviral drugs, therapeutic vaccines, or both may help to reduce heterosexual transmission. In Kenya, transmission from mother to child appears to be associated with high viral load, decreased counts of CD4-positive T cells, infection with HIV subtype C, genital shedding of virus, and maternal genetic factors. Studies are directed toward developing intervention strategies, including low-cost alternatives to prevent transmission from mother to child and new strategies to prevent sexual transmission.

Basic Science

Research by the Panels in the areas of virology, immunology, and pathogenesis continues to yield information that provides the basis for development of vaccines and therapeutic approaches. Areas of focus have included the following:

- Role of viral genes and peptides and host cytokines in HIV replication, the function of CD4-positive T cells, and pathogenesis

- Response of cytotoxic T lymphocytes (CTLs) in HIV infection and correlation with viral load

- Mucosal immunity

- Role of antibody-mediated neutralization of HIV in immunity

- Development of animal models that have contributed to the investigation of pathogenesis, vaccine development, and gene therapy approaches, including (1) a chimeric simian/human immunodeficiency virus (SHIV) model and (2) a severe combined immunodeficiency (SCID) mouse model

Differences have been observed in the viral dynamics of HIV in men and women. Study findings indicate that viral load is not predictive of disease progression in women early in infection, as has long been observed in men, suggesting that this gender-specific difference needs to be considered in making decisions about therapy for women.

HIV infection is transmitted primarily through mucosal routes. A number of studies are investigating mucosal transmission and cellular and humoral mucosal immunity. This research includes examination of the role of host factors in mucosal transmission; demonstration of intraepithelial dendritic cells as a target for infection after intravaginal exposure; demonstration that production of CD8-positive CTLs is a predominant early immune response; and investigation of the role of nasal and/or oral immunization in eliciting immune response in the vaginal or rectal mucosa.

Molecular epidemiology and genetic analysis have provided insight into the origin of lentiviruses and the evolution of the HIV epidemics in Cambodia, China, India, Myanmar, Thailand, and Vietnam. Recent data from mathematical modeling suggest that the AIDS epidemic might have begun when the ancestor virus spread from primates to one human or a small group of humans between 1910 and 1950. Genetic analysis of simian immunodeficiency virus (SIV) from primates in Africa and African HIV isolates suggests the occurrence of a recombinational event between HIV and SIV subtypes and possibly cross-species transmission. Further analysis may help to shed new light on the origin of HIV-1.

Advances in immunology include the following:

- Demonstration that responses of CD4-positive helper T cells to glycoprotein 120 (gp120) can be suppressed by the presence of gp120 antibodies that bind to the CD4 binding site

- Mapping of epitopes involved in neutralization of virus

- Observation of early but restricted CTL response to SIV infection in the rhesus macaque monkey model

- Correlation between CTL response and lowering of viral load

- Demonstration through new technology that the frequency of virus-specific CTLs in lymphatic tissue corresponds to the frequency in the more accessible peripheral blood compartment

Vaccines

As a result of new scientific findings, many new approaches to development of HIV vaccines are being pursued, and new insights have raised the expectation that improved vaccines could be developed and ready to be tested in large-scale trials in the foreseeable future. Recent research has provided new information on the structure of HIV envelope and evidence for (1) the use of decreased viral load as a measurable outcome of vaccine administration in clinical trials; (2) easier protection against viral challenges to the mucosa; (3) improved immune responses with the use of combination vaccine strategies; and (4) identification of new immunogenic epitopes that offer new targets for vaccine development. Knowledge gained from the study of long-term survivors of HIV infection indicates that the help of T cells in the maintenance of HIV-specific CTLs may be extremely important for effective control of viral load. Parallel assessment in animal models has indicated that this will be an important parameter to induce in HIV vaccines.

Research efforts of the Panels have explored issues related to (1) cross-clade recognition of HIV-1 subtypes and independence of immunotype from genotype, suggesting the potential for a broad, humoral, immune response; (2) protection of nonhuman primates challenged with virus administered to the mucosa; and (3) diverse candidates and approaches under development. Multiple vaccine approaches have been discussed. These include bacille Calmette-Guerin (BCG) and Venezuelan equine encephalitis (VEE) virus; viral-like particles; DNA vaccines; innovative adjuvants; and stimulation of mucosal immunity through both nasal and oral routes by use of new delivery techniques such as microparticles of encapsulated plasmid DNA and fusogenic liposomes prepared by fusion of liposomes with inactivated Sendai virus.

Of major importance in the development of a vaccine for HIV/AIDS is the existence throughout the world of a variety of HIV viral subtypes, and both Panels are pursuing molecular epidemiologic studies to address this issue. Ancestral sequences may prove more valuable for vaccine development than circulating strains, and such sequences are being constructed for investigation. Subtyping based on the sequence of the gp120 VP3 region and on proteins synthesized by recombinant vectors carrying the sequence has enabled the highly sensitive assay of the prevalence of subtype-specific antibodies. Several studies are identifying circulating HIV subtypes and defining the epidemiology of HIV in the Asia-Pacific region.

Nonetheless, many challenges remain, and scientific questions that need to be addressed include the following:

- Is sterilizing immunity necessary, or is partial immunity against HIV sufficient to prevent infection?

- What is the role of mucosal immunity?

- Does HIV infection prevent superinfection?

- Which parameters of immunity predict protection against infection?

Therapeutic Intervention

The dramatic decrease in morbidity and mortality in the developed world has been due primarily to the development of several classes of potent new agents and a fundamental change in the use of these agents. Continued introduction of novel antiretroviral agents has provided a wider array of drugs that can be used to overcome viral resistance and can be combined into regimens capable of achieving nearly full suppression of viral replication. The use of antiretroviral agents also has dramatically reduced the mother-to-child transmission of HIV, with a concomitant decrease in pediatric AIDS in developed countries. However, therapy remains a challenge because of the toxicity associated with long-term treatment, the development of strains resistant to one or more therapeutic agents, and expensive and complicated treatment regimens that make adherence difficult or impossible for some patients. In addition, current therapeutic agents and regimens do not eradicate HIV from the body; rather, it remains in chronically or latently infected cells. Recent work of the Panels indicates that HIV may remain attached on follicular dendritic cells for many years.
Panel research has focused on clinical evaluation of new agents and new combinations, to help in defining the optimal course of treatment, including the investigation of parameters that may be used to guide treatment options. These parameters include viral load, CD4-positive T-cell count, and measures of drug resistance. In addition, Panel researchers continue to investigate new agents, and recent reports include a promising novel protease inhibitor and a CCR5 antagonist to block entry of HIV into the host cells.

Future Goals

The AIDS Panels will continue to direct attention to the spectrum of research on HIV/AIDS, including the epidemiology and natural history of HIV disease; basic research in virology, immunology, and pathogenesis; development of diagnostic agents, therapeutic agents, and therapeutic regimens; and development of prevention interventions, including vaccines and other biomedical and behavioral interventions. In addressing these scientific topics, the Panels will continue to collaborate on symposia and workshops in addition to the regularly scheduled annual meetings.

The Panels also will continue to pursue research areas of relevance to the U.S.-Japan Common Agenda, under which the United States and Japan have agreed to use bilateral programs to address the AIDS crisis in the developing world. Of particular relevance will be efforts related to HIV vaccines and nonvaccine prevention interventions.

In 1997, the Summit of Industrial Nations (G8) met in Denver, Colorado, and declared the urgency of concerted efforts of industrialized nations to deal with the global epidemic of HIV/AIDS, especially in the developing countries. In the same year, the U.S. president announced the goal of developing a vaccine for HIV/AIDS within 10 years. The G8 Summit, which was held in Okinawa in 2000, further stressed the urgency of global HIV/AIDS efforts.

Vaccines

In response to concerns of the G8 nations, an area of great importance will continue to be development of a safe and efficacious vaccine for HIV/AIDS. This focus will include basic research in areas such as the structure of HIV envelope; genetic variation; the immune response and correlates of immune protection; development of animal models; and new strategies and approaches to vaccine design, such as novel vectors and vaccine delivery mechanisms, new vaccine target proteins, the use of whole, killed virus, and a variety of immunization strategies.

Prevention Research

The Panels will expand activities in the area of other biomedical and behavioral interventions to prevent sexual transmission, mother-to-child transmission, and transmission related to drug use. Areas of immediate attention will include development and use of microbicides and other barrier methods, further investigation of interventions to prevent mother-to-child transmission, and exploration of the theoretical basis for development of behavioral interventions.

Collaborations

The AIDS Panels will continue to use the annual meetings and other venues as opportunities to develop scientific collaborations. To advance this goal, they will endeavor to involve young scientists from both the United States and Japan in Panel activities.

The Panels, in cooperation with the Joint Committee of the U.S.-Japan Cooperative Medical Science Program and the Indian Council of Medical Research organized the 5th International Conference on Emerging Infectious Diseases in the Pacific Rim, which was held in Chennai, India, in January 2000. More than 150 participants from the United States, Japan, and countries of the Asia-Pacific region worked to identify research areas of importance for the region and problems associated with the implementation of research results in Asia-Pacific settings. Japanese and U.S. scientists will address these issues through collaborations that have been established with scientists in countries of the region, including Cambodia, China, India, Myanmar, the Philippines, Thailand, and Vietnam.

Selected References

United States

Kuroda MJ, Schmitz JE, Barouch DH, Craiu A, Allen TM, Sette A, Watkins DI, Forman MA, Letvin NL. Analysis of Gag-specific cytotoxic T lymphocytes in simian immunodeficiency virus-infected rhesus monkeys by cell staining with a tetrameric major histocompatibility complex class I/peptide complex. *J Exp Med* 1998;187:1373-81.

Lu X, Kiyono H, Lu D, Kawabata S, Torten J, Srinivasan S, Dailey PJ, McGhee JR, Lehner T, Miller CJ. Targeted lymph node immunization with whole-inactivated SIV or envelope and core subunit antigen vaccines does not reliably protect rhesus macaques from vaginal challenge with SIVmac251. *AIDS* 1998;12:1-10.

Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T, and Gray RH. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000;342:921-9.

Schooley RT, Mladenovic J, Sevin A, Chiu S, Miles SA, Pomerantz RJ, Campbell TB, Bell D, Ambruso D, Wong R, Landay A, Coombs RW, Fox L, Kamoun M, Jacovinil J. Reduced mobilization of CD34+ stem cells in advanced human immunodeficiency virus type 1 disease. *J Infect Dis* 2000;181:148-57.

Zolla-Pazner S, Dorny MK, Nyambi PN, Van Cott TC, Nadas A. Immunotyping of HIV: an approach to immunologic classification of HIV. *J Virol* 1999;73:4042-51.

Japan

Imaoka K, Miller CJ, Kubota M, McChesney MB, Lohman B, Yamamoto M, Fujihashi K, Someya K, Honda M, McGhee, JR, Kiyono H. Nasal immunization of nonhuman primates with simian immunodeficiency virus p55gag and cholera toxin adjuvant induces TH1/TH2 help for virus-specific immune responses in reproductive tissues. *J Immunol* 1998;161:55952-8.

Shinohara K, Sakai K, Ando S, Ami Y, Yoshino N, Takahashi E, Someya K, Suzaki Y, Nakasone T, Sasaki Y, Kaizu M, Lu Y, Honda M. A highly pathogenic simian/human immunodeficiency virus with genetic changes in cynomolgus monkeys. *J Gen Virol* 1999;80:1231-40.

Takehisa J, Zekeng L, Ido E, Yamaguchi-Kabata Y, Mboudjeka I, Harada Y, Miura T, Kaptu L, Hayami M. Human immunodeficiency virus type 1 intergroup (M/O) recombination in Cameroon. *J Virol* 1999;73:6810-20.

Toriyoshi H, Shioda T, Sato H, Sakaguchi M, Eda Y, Tokiyoshi S, Kato K, Nohtomi K, Kusagawa S, Taniguchi K, Shiino T, Kato A, Foongladda S, Linkanonsakul S, Oka S, Iwamoto A, Wasi C, Nagai Y, Takebe Y. Sendai virus-based production of HIV type 1 subtype B and subtype E envelope glycoprotein 120 antigens and their use for highly sensitive detection of subtype-specific serum antibodies. *AIDS Res Hum Retroviruses* 1999;15:1109-20.

Yoshimura K, Kato R, Yusa K, Kavlick MF, Maroun V, Nguyen A, Mimoto T, Ueno T, Shintani M, Falloon J, Masur H, Hayashi H, Erickson J, Mitsuya H. JE-2147: a dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1. *Proc Natl Acad Sci USA* 1999;96:8675-80.